10/509894
REC'D 13 JUL 2004
Rec'd PCT/PTO 01 OCT 2004

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZRC-MC-004	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IN 03/00133	International filing date *(day/month/year)* 01.04.2003	Priority date *(day/month/year)* 05.04.2002
International Patent Classification (IPC) or both national classification and IPC C07D231/12		
Applicant CADILA HEALTHCARE LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.10.2003	12.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schuemacher, A Telephone No. +49 89 2399-7818

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 03/00133

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-74 as originally filed

Claims, Numbers

1-21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1 (part) 9-12, 17, 18

   because:

   ☒ the said international application, or the said claims Nos. 9-12, 17, 18 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1 (part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-8,13-16,18-21
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 9-12, 17 and 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).
As already indicated in the search report (see Box I, 08.09.2003), a meaningful search covering the subject-matter of present claim 1 was impossible. The search was limited to compounds of formula (I) according to claim 1 **with the exception of any of their "analogs and their derivatives".** Since a complete search has not been carried out, any statements made in this communication with respect to novelty and inventive step are thus made in the light of those claims which were searched completely.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: Journal Of Medicinal Chemistry (2000), 43(2), 214-223
D2: Journal Of Medicinal Chemistry (1997), 40(9), 1347-1365
D3: Bioorganic & Medicinal Chemistry Letters (2001), 11(2), 165-168
D4: Bioorganic & Medicinal Chemistry Letters (1998), 8(19), 2777-2782
D5: US-A-6020343
D6: US-A-5859257
D7: WO-A-01083475

1. Novelty, Article 33(2) PCT:

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e 4-(heterocyclyl)-phenylsulfoximine compounds useful for the treatment of inflammatory diseases, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT:
The prior art documents relate to 4-(heterocyclyl)-benzenesulfonamide compounds also useful for the treatment of inflammation but which differ from the claimed compounds on account of the sulfonamide group instead of a **sulfoximine** group.
Moreover D5 discloses generically in its claim 1 the compounds which are disclaimed from

the scope of present claim 1 by a proviso "when G is "D", then at least one of X^1-X^4 is not hydrogen". Additionally, D5 does not contain specific examples of compounds with the sulfoximine group, i.e specific examples of compounds falling within the scope of present claim 1; thus, D5 does not take away the novelty of the subject-matter of the present application.

2. Inventive step, Article 33(3) PCT:

The Applicant appears to have set himself the task of making available further compounds useful for the treatment of inflammatory disease, TNF-α mediated diseases, cyclooxygenase related diseases like inflammation and pain (see p.4, l.4-6).

D5, considered to represent the most relevant state of the art, discloses 4-heterocyclyl-benzene**sulfoximine** derivatives, especially compounds wherein the heterocyclic part is furan-2-one (see claim 1 of D5) , which are explicitly disclaimed from the scope of present claim 1 by a proviso.
According to the Applicant's letter dated the 29.06.2004, the inventiveness of the present application lies in the combination of a heterocyclic part with an alkylsulfoximine group.
It is clear from the teaching of claim 4 of D7 that the heterocyclic part of these molecules (in D5, the furan-2-one ring) can also be replaced by a pyrazole, an isoxazole, an oxazole, an imidazole or an oxazolone ring. Consequently, the skilled person, looking for further anti-inflammatory agents would combine the teaching of D7 with the compounds of D5 and arrive without inventive skills to the presently claimed compounds.
Consequently, D5 can already be considered to provide a solution to the above mentioned technical problem and the new technical problem underlying the present application has therefore to be seen in the provision of anti-inflammatory agents with **unexpected advantageous effect** compared to the structurally closest compounds, in order to show convincingly that the surprising effect is indeed due to the distinguishing feature, namely the alkylsulfoximine group.
The current application contains pharmacological data proving the alleged activity on p.40, and it his letter of 29.06.04, the Applicant stated also that the current compounds does not present the drawbacks of the known anti-inflammatory agents, namely the side-effects of ulcerogenicity or cardiac problems. The claimed compounds are therefore better anti-inflammatory agents than those from the prior art and an inventive step could in principle be acknowledged for those compounds which indeed provide such surprising effects. However, it is considered that the claims should only represent a reasonable generalisation over the examples, such that all compounds falling within the scope of the claims provide a solution to the problem. If as stated in the Applicant's letter, the combination of an

alkylsulfoximine with a heterocycle confers inventiveness over the prior art, only such compounds could be claimed. However in the view of the examples provided, it appears that another essential structural feature is that R^3 is a substituted phenyl ring.
At present, it does not appear scientifically reasonable that all compounds of claim 1 possess the desired activity: the generic and open-ended terms "substituted or unsubstituted" or the extremely large number of different groups that can be X^1-X^4 and R^3-R^5 (R^1 should definitively be limited to alkyl) are certainly not considered to be appropriate and moreover not supported by the description, wherein all examples of compounds have e.g X^1-X^4 limited to a hydrogen or fluor atom and R^3 limited to a substituted phenyl ring.
The criteria of Article 33(3) PCT in conjunction with Articles 5 and 6 PCT are therefore not considered to be satisfied.

3. industrial applicability:

For the assessment of the present claims 9-12,17 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.